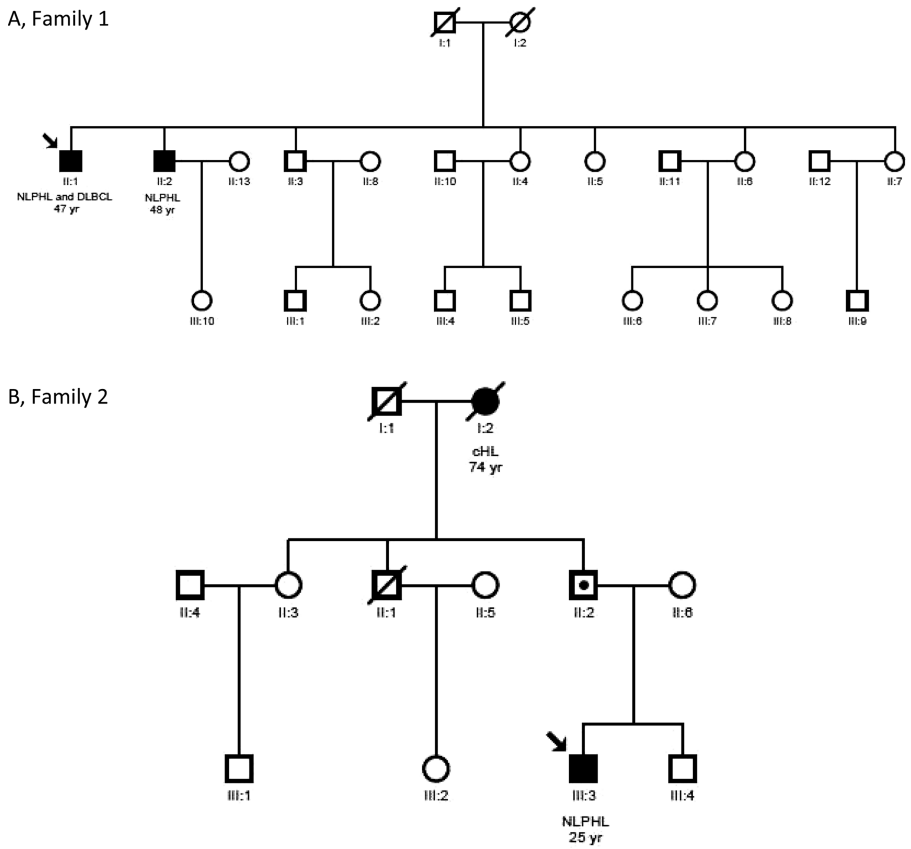

Figure 1. NLPHL family trees. (a) Pedigree of Family 1. (b) Pedigree of Family 2. Each family member is identified by pedigree number. (○) females; (□) males; (→) proband; (⊡) obligate carrier; black symbols, patients with HL; slashes through symbols, deceased individuals.

history included testicular cancer (mixed germ cells neoplasm) diagnosed in 2008 and treated with monolateral orchiectomy. His paternal grandmother (F2, I:2) was diagnosed with advanced-stage cHL at the age of 74 years and died thereafter because of disease progression.

Taking into account data from the Finnish registry [2] and the few available case-reports [3–6], the two families described in this report allow us to add some considerations. First, the obligate carrier of Family 2 (F2, II:2) is not affected by lymphoma (individual currently aged 57 years). This suggests a low penetrance of the potential predisposing gene mutation, or, alternatively, the co-existence of additional genetic or environmental factors modifying the genetic risk. Second, the earlier onset of disease in subsequent generations, as found in Family 2 (I:2, age 74 years; III:3, age 24 years), supports the concept of disease anticipation, as previously described in HL families [7]. Third, the presence of two tumors in patient F2, III:3 is an original finding in the setting of NLPHL families and might suggest a role for mutations involved in DNA repair.

In conclusion, recent findings on NLPHL families emphasize the importance of a thorough investigation of family history in patients with this subtype of HL and underline the importance of genotyping such cases to decipher the molecular basis of familial clustering.

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Haploidentical cellular therapy in elderly patients with acute myeloid leukemia: Description of its use in high risk patients

To the Editor:

Guo et al. reported an innovative approach for the treatment of acute myeloid leukemia (AML) in a 2011 issue of Blood [1]. The report showed for the first time that the infusion after chemotherapy of peripheral blood stem cells (PBSC) from haploidentical donors significantly improved the outcome in elderly AML patients, without major toxicities. After an initial engraftment, haploidentical donor cells are rejected by the host immune response. Indeed, the precise mechanism of action of this cell-therapy procedure is not fully understood and several mechanisms have been hypothesized to explain its beneficial effects: (i) donor allogeneic Natural killer (NK)- or T-cells might exert a direct cytotoxicity on leukemic cells; (ii) a

TABLE I. Patients' Characteristics

	Patient #1		Patient #2	Patient #3
Age at treatment	65		76	66
Diagnosis, WHO	Therapy related + Mixed phenotype AML		AML with myelodysplasia related changes	AML with myelodysplasia related changes
Cytogenetics	Complex karyotype		46; XY	46; XX
Comorbidity	Ovarian Ca, 6 lines of CHT		None	Obesity
Previous chemotherapy for AML	Low dose ara-C + 6-mercaptopurine		Azacitidine	None
N. of cycles (with haplo-PBSC)	**2**		**1**	**1**
	1 st cycle	2nd cycle	1 st cycle	1 st cycle
N. of CD34+ cells infused	1×10^6/Kg	1×10^6/Kg	3×10^6/Kg	$2{,}5\times10^6$/Kg
N. of CD3+ cells infused	$0{,}7\times10^8$/Kg*	$0{,}7\times10^8$/Kg	$0{,}86\times10^8$/Kg	1×10^8/Kg
N. of CD56+ cells infused	nd	nd	$0{,}18\times10^8$/Kg	$0{,}13\times10^8$/Kg
Time to ANC > 500/μL	19	17	45	11
Time to Plts >50.000/μL	17	18	no recovery for plts	18
Microchimerism	Yes	Yes	No	No
GVHD (acute or chronic)	No	No	No	No
Transplant related toxicity	Neutropenic Fever with Pneumonia	Neutropenic fever	Neutropenic Fever, Ototoxicity (amikacina)	Fungal endophtalmitis and chronic sinusitis
Response after first cycle	PR*	CR	Refractory	CR
Survival (from 1st PBSC infusion)	6 months		3 months	10 months
Status at last follow up	Dead of disease		Dead of disease	Alive in CR

* PR defined as: all hematologic criteria of CR and decrease of pretreatment bone marrow blast percentage by at least 50%.
nd: not determined.

proinflammatory effect of the allogeneic host–donor interaction might trigger an autologous antitumor immunity; and (iii) cell-therapy might induce modifications in leukemic cells or in stromal/vascular cells that ultimately elicit an autologous immune responses.

So far, the data obtained, Guo et al. have not been confirmed by other groups worldwide. We recently treated with this protocol three elderly patients with high-risk AML. Compared to the Chinese experience, the patients were all affected by high-risk AML. As summarized in Table I, Patient #1 had treatment-related AML following prolonged chemotherapy (six total lines) for ovarian cancer and her blasts had a mixed phenotype with complex karyotype. Patients #2 and #3 had AML with myelodysplasia-related changes, one of them (Patient #2) had received four azacitidine courses, with poor response and worsening of both hematological and clinical conditions.

Institutional ethics approval was obtained for the use of this treatment protocol. All three patients received an induction regimen (a "3+7" regimen with mitoxantrone and ara-C) followed by the infusion of Granulocyte colony-stimulating Factor (G-CSF)-mobilized PBSC from haploidentical familial donors, according to the original protocol [1]. The potential reactivity of patient T-cells against their haploidentical counterparts was proved in vitro by mixed lymphocyte reaction. This in vitro reactivity resulted in vivo in graft-rejection, with detectable microchimerism in only one patients and absence of acute or chronic Graft versus Host Disease (GVHD) in all patients. As detailed in Table I, Patient #1 had a partial response, with Bone Marrow (BM) blast reduction from 90 to 45%. She then received an intensified salvage regimen (high-dose ara-C and idarubicin plus cyclosporine to overcome Minimal Residual Disease (MRD) resistance) [2], followed by a second infusion of haploidentical PBSC. After this cycle, she had a complete hematological recovery, and the BM aspirate showed complete remission of disease at flow cytometry. Six weeks later, AML relapsed; the patient was not further treated and died shortly thereafter. Patient #2 and #3 received 1 infusion of haploidentical PBSC after induction chemotherapy. Patient #2 was refractory, he refused further treatment and died few weeks later. Patient #3 achieved Complete Remission (CR); however, she was unable to receive consolidation therapy due to the development of fungal endophthalmitis and chronic sinusitis by Fusarium. She completely recovered within 3 months, with a mild residual chronic renal insufficiency. Despite lack of consolidation therapy, she is still in CR at 11 months of follow up.

Our observation in high-risk elderly AML patients confirms that infusion of haploidentical-mobilized PBSC following induction chemotherapy is feasible and safe. Compared to Guo et al. [1,3], we applied the strategy in AML patients with very unfavorable prognosis, two of them previously treated either with multiple chemotherapy lines or with repeated azacitidine courses. In spite of previous treatments, the haploidentical infusion did not induce acute GVHD. Considering the presenting features, the achievement of CR in two of three patients was encouraging and somehow unexpected, especially for the long-surviving patient who achieved CR after a single course of chemotherapy followed by haploidentical PBSC infusion. Finally, the two patients achieving CR had a leukothrombocytopenia duration shorter than one might have expected, suggesting a possible role of the infused cells in favoring hematopoietic recovery. We conclude that the "nonengraftment haploidentical cell-therapy" is feasible also in high-risk and previously treated AML patients, although the real efficacy in this setting needs to be further investigated [4]. Indeed, based on our preliminary experience, a prospective trial will be launched soon to evaluate the procedure in elderly AML patients, including AML secondary to myelodysplasia, either untreated or after azacytidine, therapy-related AML as well as de novo AML

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Conflict of interest: Nothing to report.

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